http://www.kidney-international.org

Results of a randomized controlled trial on statin use in dialysis patients had no influence on statin prescription

Ngan N. Lam[1], Arsh K. Jain[1], Dan G. Hackam[2,3], Meaghan S. Cuerden[1], Rita S. Suri[1], Cindy Y. Huo[4], Ping Li[4], William F. Clark[1] and Amit X. Garg[1,3,4]

[1]Division of Nephrology, Department of Medicine, University of Western Ontario, London, Canada; [2]Division of Clinical Pharmacology, Department of Medicine, University of Western Ontario, London, Canada; [3]Department of Epidemiology and Biostatistics, University of Western Ontario, London, Canada and [4]Institute for Clinical Evaluative Sciences, Toronto, Canada

Randomized trials provide high-quality evidence for patient care. The Der Deutsche Diabetes Dialyse Studie (4D), a randomized study which demonstrated no benefit of statins among diabetic patients receiving hemodialysis, was published in July 2005. To determine effects of this study we conducted a retrospective, population-based, time series analysis with change-point regression to see if the rate of statin prescription to dialysis patients had been modified. We linked health administrative data for all diabetic hemodialysis patients living in Ontario, Canada, with similar characteristics to the 4D patient cohort. During the nearly 11-year period prior to study publication, the rate of statin use increased almost 14-fold, from 43 to 597 per 1000 patients. For 2.5 years after study publication, rather than diminish, statin use continued to rise to an absolute rate of 676 per 1000 patients. These temporal patterns in statin use closely mimicked trends in the diabetic population not receiving dialysis. The 4D trial had no impact on statin use when we restricted the analysis to incident statin prescriptions or expanded the characteristics of the dialysis patients considered for study. Thus, we found that publication of a large, expensive, randomized controlled trial in patients receiving hemodialysis had no immediate impact on clinical practice. The use of a common cardiovascular medication in this patient population appears to be influenced by other factors.

Kidney International (2009) **76,** 1172–1179; doi:10.1038/ki.2009.323; published online 23 September 2009

KEYWORDS: diabetes; evidence uptake; hemodialysis; statins

Correspondence: *Amit X. Garg, London Kidney Clinical Research Unit, Department of Medicine, University of Western Ontario, Room ELL-101, Westminster Tower, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, Canada N6A 4G5. E-mail: amit.garg@lhsc.on.ca*

Received 1 March 2009; revised 28 May 2009; accepted 7 July 2009; published online 23 September 2009

The goal of clinical research is to improve patient health through the development of new medical knowledge. Randomized trials are considered the gold standard for providing knowledge on the utility, benefits, and harms of an intervention.[1] Studies in the general population have shown that the publication of a large trial can influence physician care practices.[2–5] For example, there was a sudden, dramatic increase in the number of prescriptions for ramipril after the release of the Heart Outcomes Prevention Evaluation trial, which showed clear benefit in the secondary prevention of cardiovascular disease.[4] Similarly, there was a sudden decline in estrogen replacement therapy prescribing after publication of the Women's Health Initiative, which found health risks associated with the use of combined estrogen and progestin.[3] In both cases, changes in prescribing occurred within months after trial publication.

Unfortunately, compared with other disciplines, there is a paucity of high quality randomized data in patients with kidney diseases (including those receiving dialysis).[6] In addition, systematic reviews suggest that such patients are routinely excluded from large cardiovascular trials.[7] In the absence of renal trial data, some nephrologists are accustomed to placing a greater emphasis on other types of evidence or weighing trial evidence from the general population to a greater degree. When interventions are tested in patients with kidney disease only after proving effective in the general population, discordant results among trials may leave some physicians puzzled as to what to do. All of these considerations make the uptake of evidence from large renal trials uncertain. One of the largest randomized controlled trials ever published in nephrology is Der Deutsche Diabetes Dialyse Studie (4D), which showed no beneficial effect of statins in diabetic patients receiving hemodialysis.[8] We sought to determine whether there was a change in statin use among diabetic patients on dialysis after the publication of 4D.

RESULTS

Baseline characteristics

In September 1994, there were 115 diabetic patients receiving hemodialysis in Ontario who met the criteria of being similar to the 4D population. By September 2007, this number had increased to 595 patients. The number of diabetic patients not receiving dialysis was 114,263 in 1994 and 242,209 in 2007.

Baseline characteristics are summarized in Table 1. The mean age for Ontario diabetic patients on hemodialysis in this study was higher than the mean age for German diabetic patients on hemodialysis in 4D (73 years vs 66 years old). This was not surprising given that we excluded patients in Ontario who were less than 66 years of age to ensure that all patients were eligible for coverage under the provincial drug plan. The proportion of women studied was similar. However, the duration of dialysis was longer and cardiovascular disease was less prevalent in Ontario.

Table 1 | Characteristics of diabetic hemodialysis patients in Ontario and in Der Deutsche Diabetes Dialyse Studie (4D) trial

	Ontario[a]	4D trial[b]
Sample size	595	1255
Age, years	73	66
Women, %	45	46
Time receiving dialysis, months	14	8
History of cardiovascular disease[c]		
Myocardial infarction	9	17
Congestive heart failure	21	35

Means presented for continuous measures and percentages for categorical measures.
[a]Patient characteristics for Ontario are reported for the last time interval (1 September 2007 to 31 December 2007).
[b]We performed a weighted average of placebo and atorvastatin groups to derive the patient characteristics of the 4D trial.
[c]Those with a history of a cardiac event or cardiac intervention in the previous 3 months were excluded from Ontario and the 4D trial. In Ontario, conditions were assessed with administrative database codes as described in Supplementary Appendices B and C, using data available in 3 the years before study entry. This differs from 4D, where conditions were assessed directly from patients and their medical charts.

Primary analysis

Before the publication of 4D, from September 1994 to July 2005, the rate of statin use dramatically increased 13.9-fold from 43 to 597 per 1000 diabetic patients on hemodialysis. After the publication of 4D, rather than diminishing, statin use continued to rise to a rate of 676 per 1000 patients by December 2007. This represented a further 1.1-fold increase in the rate of statin use. Using regression analysis, the age and sex standardized rate of statin use per 1000 diabetic hemodialysis patients increased by 51.2 annually (95% confidence interval (CI), 50.7–51.9) before 4D. After 4D, the rate increased by 40.6 per 1000 annually (95% CI, −1.8 to 82.8). The slopes of the lines before and after 4D were not statistically different. These temporal patterns in statin use mimicked trends in the comparison group of diabetic patients not receiving dialysis (Figure 1).

Additional analyses

Der Deutsche Diabetes Dialyse Studie had no impact on statin use when we restricted the analysis to incident statin prescriptions, prescriptions written by nephrologists, or expanded the range of dialysis patients considered. The results were no different in multiple other sensitivity analyses. In the year 2007, the annual cost of the statin prescriptions per 1000 diabetic patients receiving hemodialysis was 490,424 dollars CAD (496,330 dollars US).

DISCUSSION

Despite statin trials in the general population excluding patients with renal disease, the use of statins in diabetic patients on hemodialysis in Ontario increased by more than

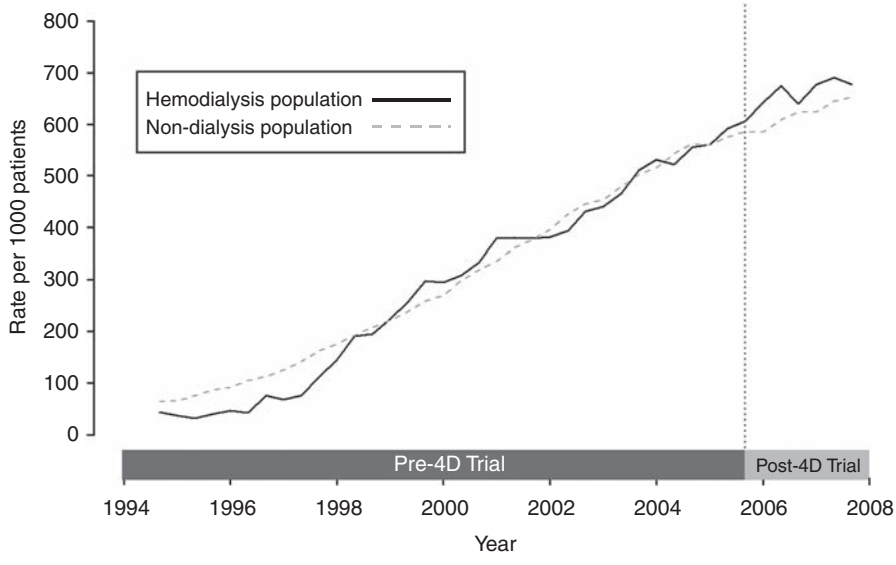

Figure 1 | Statin use in diabetic patients receiving and not receiving hemodialysis.

13.9-fold over a decade from 1994 to 2005. This dramatic increase remained evident when only new statin prescriptions were considered, and when the ordering physician was a nephrologist. In July 2005, the 4D trial was published in a high impact journal. To date, 4D has been one of the largest published randomized controlled trials on the effect of statins in hemodialysis patients. Contrary to most statin trials in the general population, this trial failed to show a statistically significant benefit of atorvastatin in preventing cardiovascular events in diabetic patients on hemodialysis.[8] Despite this negative result, however, this trial had no apparent impact on prescribing practice in Ontario. The rate of statin use in diabetic hemodialysis patients continued to increase by another 1.1-fold over the 2 years after the publication of 4D.

There are several potential explanations as to why physicians did not reduce their statin prescribing behavior in response to 4D. First, as shown in Table 2, there were many clinical studies showing the beneficial effects of statins on cardiovascular outcomes in other populations.[9–17] It is possible that physicians doubted the results of 4D for various reasons and placed greater importance on the evidence from observational studies involving dialysis patients or randomized trials involving the general population. At present, there are two ongoing large trials assessing the effect of statins on major cardiovascular events in patients with advanced renal disease: AURORA[18] (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis, recruited 2775 patients) and SHARP[19] (Study of Heart And Renal Protection, recruited 9000 patients, simvastatin plus ezetimibe is the regime being tested). Physicians may be waiting for the completion of these trials before deciding to make a change to their current clinical practice.

Second, a neutral trial where the results do not show a statistically significant effect with either a distinct harm or benefit may be discounted by physicians. As shown with the Heart Outcomes Prevention Evaluation trial and the Women's Health Initiative, trials which show strong evidence of benefit or harm from a treatment have dramatically changed prescribing practices.[3,4] Although in 4D there was an increased risk of fatal stroke in the statin treatment group compared with the placebo group (relative risk of 2.03; 95% CI, 1.05–3.93; $P = 0.04$),[8] the authors suggest that this may have been a chance finding given the results of the CARDS (Collaborative Atorvastatin Diabetes Study) trial which showed that atorvastatin reduced stroke by 48% (95% CI, 11 to 69%).[12]

Third, despite 4D being a multicentered trial, it was only conducted in a single country, Germany. It is very possible that 4D impacted clinical practices in Germany due to local influential physicians, which did not translate to Canada. If this is true, then the AURORA and SHARP trials, which are recruiting patients and engaging investigators in multiple countries, including Canada, may have a larger global influence.

Finally, the inertia of previous practice may also be contributing to the lack of expected response after 4D. A patient's cardiovascular and diabetic medication regimen while on dialysis is strongly influenced by the medications they were receiving before dialysis, which are frequently prescribed by physicians other than nephrologists. Nephrologists may be reluctant to discontinue statin therapy if it was initiated before dialysis treatment, and particularly if it was started by another physician. However, in our study, there was no difference in the results when we restricted the analysis to incident statin use. Diabetic patients on dialysis are also likely to have multiple physicians involved in their ongoing care, including nephrologists, endocrinologists, and cardiologists. Although the results of the 4D trial may be familiar to nephrologists, it is possible that other providers were less familiar or influenced by its results. However, again, when we restricted the analysis to statins only prescribed by nephrologists, the results were no different.

Our study has many strengths. It is a large, population-based assessment of statin use in patients over the age of 65 receiving dialysis over the span of 13 years in Canada's largest province. The same methods were used to compare the results to the general population over the same time period. We used validated codes and methods to ascertain the patient population, baseline characteristics, and outcomes. Finally, we confirmed the findings were robust in a number of additional analyses. However, there are some limitations to our study which merit consideration. Although we tried to model our Ontario patient population to closely match the population in the 4D trial, we were not able to fully apply the 4D inclusion and exclusion criteria given the limitations of administrative data; in particular, there was an age difference between the two samples. Also, it was not possible to evaluate the extent to which other potential factors, such as pharmaceutical marketing, influenced prescribing patterns.

In conclusion, the publication of a large, expensive randomized controlled trial in patients receiving hemodialysis had no apparent effect on clinical practice. Growth in statin prescribing, both before and after the trial, confirms the use of common cardiovascular medications in this patient population is influenced by other factors. It remains to be seen how other high profile renal trials testing interventions commonly used in the general population will impact clinical practice in the future.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective, population-based, interventional analysis that used several linked health-care databases in Ontario, Canada from 1 September 1994 to 31 December 2007. Each year was divided into three 4-month intervals (January to April, May to August, and September to December), for a total of 40 consecutive intervals in the time series. Baseline characteristics were assessed within the 3 years preceding each interval. Ontario is Canada's most populous and ethnically diverse province (38% of the Canadian population) with more than 12 million residents, of whom 77% are Caucasian, 51% are female, 1.6 million are 65 years of age or older (Statistics Canada, 2006 Census), over 800,000 (8.8%) are diabetic,[20] and 8677 are receiving dialysis (7127 hemodialysis, 1550 peritoneal

Table 2 | Key statin publications and guidelines from 1994 to 2007: randomized controlled trials, observational studies, and clinical practice guidelines

Date	Landmark statin trials with renal exclusion criteria noted, if any	Clinical practice guidelines
November 1994	4S (*n*=4444): simvastatin was beneficial in patients with MI for secondary prevention.[9]	
November 1995	WOSCOPS (*n*=6595): pravastatin was beneficial in patients for primary prevention of coronary heart disease.[17] Excluded 'creatinine >155 μmol/l' (>1.76 mg/dl)[29]	
October 1996	CARE (*n*=4159): pravastatin was beneficial in patients with MI for secondary prevention.[15] Excluded 'nephrotic syndrome or other renal disease'[30] (2+ proteinuria or greater on routine dipstick testing or serum creatinine values >1.5 times the upper limit of normal as defined by the central study laboratory).	
May 1998	AFCAPS/TexCAPS (*n*=6605): lovastatin was beneficial in patients for primary prevention of acute major coronary events.[13] Excluded 'nephrotic syndrome'.[31]	
November 1998	LIPID (*n*=9014): pravastatin was beneficial in patients with acute coronary syndrome for secondary prevention.[10] Excluded 'renal disease'.[32]	
September 1999		AHA: for patients with diabetes, the primary goal of therapy is to reduce the LDL-C levels to ⩽100 mg/dl (⩽2.59 mmol/l) by adding drug therapy, when necessary, to maximal dietary therapy. Statins are first-line therapy to achieve an LDL-C of ⩽100 mg/dl (⩽2.59 mmol/l).[33]
May 2001		NCEP ATP III Executive Summary: for patients with CHD or CHD risk equivalents, the LDL goal is <100 mg/dl (<2.59 mmol/l) and LDL-lowering drug therapy, usually with a statin, should be considered when LDL ⩾130 mg/dl (⩾3.36 mmol/l).[34]
January 2002	USRDS Dialysis Morbidity and Mortality Wave II (*n*=3716): statins reduced cardiovascular-specific death and total mortality in dialysis (peritoneal dialysis and hemodialysis) patients (observational study).[35]	
May 2002		AHA Executive Summary: for patients with diabetic dyslipidemia, LDL lowering, usually with statins, is the primary target to achieve an optimal level of ⩽100 mg/dl (⩽2.59 mmol/l).[36]
July 2002	HPS (*n*=20,536): simvastatin was beneficial in high-risk patients for secondary prevention of major vascular events (mortality and fatal/non-fatal vascular events).[11] Excluded 'severe renal disease or evidence of impaired renal function (creatinine >2.3 mg/dl (>200 μmol/l))'.[11]	
November 2002	PROSPER (*n*=5804): pravastatin reduced the risk of coronary disease in elderly patients with a history of, or risk factors for, vascular disease.[37] Excluded patients with 'serum creatinine >200 μmol/l (>2.3 mg/dl)'.[38]	
December 2002	ALLHAT-LLT (*n*=10,355): pravastatin, compared to usual care, did not significantly reduce all-cause mortality or combined fatal and nonfatal CHD in older patients with well-controlled hypertension and moderately elevated LDL-C.[39] Excluded patients with 'serum creatinine >2 mg/dl (>176.8 μmol/l)'.[39]	NCEP ATP III Final Report: persons with established CHD should receive intensive LDL-lowering therapy. The goal of therapy in persons with established CHD should be LDL cholesterol <100 mg/dl (<2.59 mmol/l). Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals.[40]
January 2003	CARE *post hoc* subgroup analysis (*n*=1711): pravastatin is effective and safe for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency (creatinine clearance ⩽75 ml/min (⩽1.25 ml/s) using the Cockcroft-Gault equation).[41]	
April 2003	ASCOT-LLA (*n*=10,305): atorvastatin was beneficial in patients with hypertension in reducing major cardiovascular events.[16]	KDOQI: consider treatment for patients with stage 5 CKD and LDL⩾100 mg/dl (⩾2.59 mmol/l) or fasting TG⩾200 mg/dl (⩾2.26 mmol/l) and non-HDL cholesterol LDL⩾130 mg/dl (⩾3.36 mmol/l).[42]
July 2004		NCEP ATP III: In high-risk persons, the recommended LDL-C goal is <100 mg/dl (<2.59 mmol/l). An LDL-C goal of <70 mg/dl

Table 2 | Continued

Date	Landmark statin trials with renal exclusion criteria noted, if any	Clinical practice guidelines
		(<1.81 mmol/l) is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk. If LDL-C is ⩾100 mg/dl (⩾2.59 mmol/l), an LDL-lowering drug is indicated simultaneously with lifestyle changes. If baseline LDL-C is <100 mg/dl (<2.59 mmol/l), institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dl (<1.81 mmol/l) is a therapeutic option on the basis of available clinical trial evidence.[43]
August 2004	CARDS (*n*=2838): atorvastatin was beneficial in patients with type 2 diabetes for primary prevention of first cardiovascular disease events, including stroke.[12] Excluded 'severe renal dysfunction or nephrotic syndrome or creatinine >150 μmol/l' (>1.7 mg/dl).[44]	
January 2005	DOPPS (*n*=7365): statins reduced cardiovascular-specific mortality and all-cause mortality in hemodialysis patients (observational study).[45]	
April 2005	TNT (*n*=10,001): high-dose atorvastatin was beneficial in patients with stable coronary heart disease for secondary prevention.[14] Excluded 'nephrotic syndrome'.[46]	
July 2005	4D (*n*=1255): atorvastatin had no significant effect on the composite primary end point in patients with diabetes receiving hemodialysis.[8]	
August 2005		IDF Global Guideline for Type II Diabetes: recommendations for the standard care of cardiovascular risk protection includes providing active management of all blood lipid profile and statin treatment at standard dose for all patients >40 years old (or all with declared cardiovascular disease) or >20 years old with microalbuminuria or assessed as being at particularly high risk. (IDF, 2005)
May 2006		CHEP: statin therapy is recommended in hypertensive patients with 3 or more cardiovascular risk factors.[47]
September 2006		CCS: for those low- and moderate-risk individuals who are candidates for statin therapy, treatment to lower LDL-C by at least 40% is generally appropriate. In high-risk individuals, treatment should be started immediately and concomitantly with diet and exercise. The treatment goal for most high-risk patients is to achieve an LDL-C of less than 77.3 mg/dl (2.0 mmol/l); an optimal reduction in LDL-C for most CAD patients is at least 50%.[48]
January 2007		AHA/ADA: in individuals with diabetes who are over the age of 40 years, without overt CVD, but with 1 or more major CVD risk factors, the primary goal is an LDL-C level <100 mg/dl (<2.59 mmol/l). If LDL-lowering drugs are used, a reduction of at least 30% to 40% in LDL-C levels should be obtained. If baseline LDL-C is <100 mg/dl (<2.59 mmol/l), statin therapy should be initiated based on risk factor assessment and clinical judgment. In individuals with diabetes who are under the age of 40 years, without overt CVD, but who are estimated to be at increased risk of CVD either by clinical judgment or by risk calculator, the LDL-C goal is <100 mg/dl (<2.59 mmol/l), and LDL-lowering drugs should be considered if lifestyle changes do not achieve the goal.[49]
February 2007		KDOQI: treatment with a statin should not be initiated in patients with type II diabetes on maintenance hemodialysis who do not have a specific cardiovascular indication for treatment.[21]

4D, Der Deutsche Diabetes Dialyse Studie; 4S, Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; AHA, American Heart Association; ADA, American Diabetes Association; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid-Lowering Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial, Lipid-Lowering Arm; ATP III, Adult Treatment Panel III; CAD, Coronary Artery Disease; CHD, Coronary Heart Disease; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events; CCS, Canadian Cardiovascular Society; CVD, Cardiovascular Disease; CHEP, Canadian Hypertension Education Program; DOPPS, Dialysis Outcomes and Practice Patterns Study; HDL, high-density lipoprotein; HPS, Heart Protection Study; IDF, International Diabetes Federation; KDOQI, Kidney Disease Outcomes Quality Initiative; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LIPID, long-term intervention with pravastatin in ischemic disease; MI, myocardial infarction; NCEP, National Cholesterol Education Program; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; TNT, treating to new targets; USRDS, United States Renal Data System; WOSCOPS, West of Scotland Coronary Prevention Study.

dialysis) (Canadian Organ Replacement Register, 2005). Emigration from the province is less than 1% per year (Ontario Ministry of Finance, Ontario Population Projections Update, 2007). Ontarians have access to health care and those 65 years of age and older also have their prescription medications paid for by a universal government plan. This study was conducted according to a prespecified protocol, and ethics approval was obtained from the institutional review board at Sunnybrook Health Sciences Centre (Toronto, Canada).

Intervention

Der Deutsche Diabetes Dialyse Studie is currently the only randomized trial to examine the effect of statin use on cardiovascular outcomes in patients receiving maintenance hemodialysis.[8] This prospective, multicenter, double-blind trial recruited 1255 German chronic hemodialysis patients with type II diabetes who were randomized to receive either atorvastatin 20 mg/day or placebo. The trial cost was approximately 24 million CAD dollars (15 million US dollars, 17 million Euros) (C. Wanner, 2008, personal communication). The results showed that atorvastatin did not significantly reduce the primary end point of cardiovascular death, non-fatal myocardial infarction, or stroke. In a secondary analysis, there was an unexpected increase in fatal strokes in the atorvastatin group compared with those receiving placebo. The trial investigators concluded that 'in persons with type II diabetes mellitus who are receiving maintenance hemodialysis and have low-density lipoprotein cholesterol values between 80 and 190 mg per deciliter (2.07 and 4.92 mmol/l), routine treatment with a statin to reduce the primary end point of death from cardiac causes, myocardial infarction, and stroke is not warranted.'[8] The results were initially presented at the American Society of Nephrology (ASN) Annual Meeting in October 2004 and the trial was published on 21 July 2005 in the New England Journal of Medicine. In 2007, the American National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) changed their clinical practice guidelines to recommend that 'treatment with a statin should not be initiated in patients with type II diabetes on maintenance hemodialysis who do not have a specific cardiovascular indication for treatment.'[21] No Canadian guidelines for dialysis patients were published on this topic. In this study, we specified the publication date of 4D (21 July 2005) as the primary time point to assess whether there was a change in prescribing practice.

Data sources

We determined drug use by accessing the Ontario Drug Benefit (ODB) administrative database, which records outpatient prescription claims for all patients older than 65 years. This included all medications in the statin drug class (Supplementary Appendix A). To be covered, a prescription medication must be resupplied at least every 100 days, which is why we used time series intervals of 4 months. We identified dialysis patients using the Ontario Health Insurance Plan (OHIP) database. We determined baseline characteristics of age and gender using the Registered Persons Database (RPDB). Finally, we determined diagnostic and procedural information from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), which documents all hospitalizations and includes up to 16 diagnoses and 25 procedures for each admission. We used database codes with proven validity as detailed in Supplementary Appendix B. All of these data source have been successfully used in previous studies to examine prescribing rates of statins and a number of other medications in Ontario.[3–5,22,23]

Population

At the beginning of each 4-month interval, we considered all diabetic hemodialysis patients living in Ontario, Canada who were similar to patients recruited into 4D. Eligible patients were restricted to those aged 66 years and older to allow for the presence of Ontario drug coverage for at least an entire previous year. As was carried out in 4D, we excluded patients older than 80 years, as well as those with a cardiovascular event in the preceding 3 months (namely a hospital encounter for vascular intervention, congestive heart failure, or myocardial infarction). Also in keeping with 4D, we excluded those receiving hemodialysis for more than 2 years. Those receiving hemodialysis for less than 90 days were also excluded, to eliminate those who may have received hemodialysis for potentially reversible acute kidney injury. Finally, we also excluded patients who had evidence of a renal transplant or peritoneal dialysis in the preceding 3 months. A detailed description of the algorithm used to define maintenance hemodialysis is provided in Supplementary Appendix C. An example of how the exclusion criteria were applied for each interval is provided in Supplementary Appendix D.

Primary analysis

The primary study outcome was the rate of statin prescriptions filled in each 4-month interval per 1000 patients. Patients who filled more than one statin prescription in a given interval were only counted once.

Additional analyses

We conducted several sensitivity analyses to test the robustness of our results. First, we restricted the analysis to incident statin use by excluding patients who filled a statin prescription in the preceding year. Second, we restricted the statin prescriptions to those where the ordering physician was a nephrologist. Third, we changed the characteristics of dialysis patients by varying the criteria to include those without diabetes, those on dialysis for greater than 2 years, those older than 80 years of age, and those with a cardiovascular event in the preceding 3 months. Finally, we provided the annual cost of the statin prescriptions (as paid for by the drug benefit program for each patient). We did not include any co-payments made by Ontario residents, which were small in nature.

Comparison group

For comparison, we also examined statin use in diabetic patients in Ontario who met the same eligibility criteria with the exception that they were not receiving dialysis. To help interpret secular changes in statin use, we summarized the publication of 15 landmark statin trials, as well as the introduction of 11 practice guidelines related to statin therapy, spanning 1994 to 2007 (Table 2). Guidelines were in the fields of diabetes, hypertension, cardiovascular disease, and renal disease.

Statistical analysis

Change-point regression was used to determine whether there was a difference in the age and sex standardized rate of statin use before and after 4D.[24,25] As data were collected every 4 months, and 4D was published on 21 July 2005, we defined the change-point as occurring at the third period of the year beginning 1 September 2005. There were 33 periods before 4D and 7 periods after. The design matrix is

described elsewhere.[24] The annual increase in statin use and 95% CIs were estimated using linear regression. We used an F-test to determine whether there was difference in slope before and after 4D.[24] Statistical assumptions for the linear model were met; specifically, the Durbin–Watson statistic for autocorrelation was reviewed and auto-correlations and inverse and partial autocorrelations were visually inspected; a first-order autoregressive parameter was included if the Durbin–Watson test statistic was significant.[26,27] Multiple sensitivity analyses were performed: excluding the first 12 observations, examining non-age and sex standardized rates, and performing the analysis with another model (interventional autoregressive integrated moving-average (ARIMA) time series models with a step function).[28] Results were considered statistically significant at the 0.05 level using two-tailed tests. Statistical analyses were performed using SAS statistical software, version 9.1.3 (SAS Institute, Cary, NC, USA) and R version 2.6.1, (The R Foundation for Statistical Computing). Graphs were generated using R version 2.6.1 and PowerPoint 2003 (Microsoft, Redmond, WA, USA).

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This project was supported by the Lawson Health Research Institute and the Physicians' Services Incorporated Foundation. DGH was supported by clinician scientist salary funding from the University of Western Ontario. RSS was supported by a Canadian Institutes of Health Research Randomized Controlled Trials Mentorship Award. AKJ was supported by a Clinician Investigator Program Award from the University of Western Ontario and a Fellowship Award from the Canadian Institutes of Health Research. AXG was supported by a Clinician Scientist Award from the Canadian Institutes of Health Research. The Institute for Clinical Evaluative Sciences receives funding from the Ontario Ministry of Health and Long-term Care. The opinions, results, and conclusions reported in this paper are those of the authors and are independent of the funding sources. We thank Michael Paterson and Ian McLeod for their help and support.

SUPPLEMENTARY MATERIALS

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Stel VS, Jager KJ, Zoccali C *et al.* The randomized clinical trial: an unbeatable standard in clinical research? *Kidney Int* 2007; **72**: 539–542.
2. Jackevicius CA, Anderson GM, Leiter L *et al.* Use of the statins in patients after acute myocardial infarction: does evidence change practice? *Arch Intern Med* 2001; **161**: 183–188.
3. Austin PC, Mamdani MM, Tu K *et al.* Prescriptions for estrogen replacement therapy in Ontario before and after publication of the Women's Health Initiative Study. *JAMA* 2003; **289**: 3241–3242.
4. Tu K, Mamdani MM, Jacka RM *et al.* The striking effect of the Heart Outcomes Prevention Evaluation (HOPE) on ramipril prescribing in Ontario. *CMAJ* 2003; **168**: 553–557.
5. Mamdani MM, Tu JV. Did the major clinical trials of statins affect prescribing behaviour? *CMAJ* 2001; **164**: 1695–1696.
6. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. *J Am Soc Nephrol* 2004; **15**: 411–419.
7. Coca SG, Krumholz HM, Garg AX *et al.* Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA* 2006; **296**: 1377–1384.
8. Wanner C, Krane V, Marz W *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
9. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–1389.
10. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; **339**: 1349–1357.
11. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
12. Colhoun HM, Betteridge DJ, Durrington PN *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**: 685–696.
13. Downs JR, Clearfield M, Weis S *et al.* Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; **279**: 1615–1622.
14. LaRosa JC, Grundy SM, Waters DD *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425–1435.
15. Sacks FM, Pfeffer MA, Moye LA *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335**: 1001–1009.
16. Sever PS, Dahlof B, Poulter NR *et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**: 1149–1158.
17. Shepherd J, Cobbe SM, Ford I *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**: 1301–1307.
18. Fellstrom B, Holdaas H, Jardine AG *et al.* Effect of rosuvastatin on outcomes in chronic haemodialysis patients: baseline data from the AURORA study. *Kidney Blood Press Res* 2007; **30**: 314–322.
19. Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* 2003; **63**: S207–S210.
20. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. *Lancet* 2007; **369**: 750–756.
21. Kidney Disease Outcomes Quality Initiative. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. *Am J Kidney Dis* 2007; **49**: S12–S154.
22. Levy AR, O'Brien BJ, Sellors C *et al.* Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003; **10**: 67–71.
23. Austin PC, Mamdani MM, Tu K. The impact of the Women's Health Initiative study on incident clonidine use in Ontario, Canada. *Can J Clin Pharmacol* 2004; **11**: e191–e194.
24. Julious SA. Inference and estimation in the change point regression problem. *Journal of the Royal Statistical Society, Series D (The Statistician)* 2001; **50**: 51–61.
25. Quandt R. The estimation of the parameters of a linear regression system obeying two separate regimes. *J Am Stat Assoc* 1958; **53**: 873–880.
26. Brocklebank JC, Dickey DA. *SAS for Forecasting Time Series*, 2nd edn. SAS Institute Inc.: Cary, NC, 2003.
27. Kleinbaum D. *Applied regression analysis and other multivariable methods*, 3rd edn. Duxbury: Pacific Grove, CA.
28. Hipel K, McLeod A. Time series modelling of water resources and environmental systems. *Developments in Water Science*. Elsevier: Maryland Heights, MD, 1994, p. 684.
29. The West of Scotland Coronary Prevention Study Group. A coronary primary prevention study of Scottish men aged 45-64 years: trial design. *J Clin Epidemiol* 1992; **45**: 849–860.
30. Sacks FM, Pfeffer MA, Moye' L *et al.* Rationale and design of a secondary prevention trial of lowering normal plasma cholesterol levels after acute myocardial infarction: the Cholesterol and Recurrent Events trial (CARE). *Am J Cardiol* 1991; **68**: 1436–1446.
31. Downs JR, Beere PA, Whitney E *et al.* Design & rationale of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol* 1997; **80**: 287–293.
32. The LIPID Study Group. Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) Study: a randomized trial in patients with previous acute myocardial

infarction and/or unstable angina pectoris. *Am J Cardiol* 1995; **76**: 474–479.
33. Grundy SM, Benjamin IJ, Burke GL *et al.* Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999; **100**: 1134–1146.
34. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation,
And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
35. Seliger SL, Weiss NS, Gillen DL *et al.* HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. *Kidney Int* 2002; **61**: 297–304.
36. Grundy SM, Howard B, Smith Jr S *et al.* Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. *Circulation* 2002; **105**: 2231–2239.
37. Shepherd J, Blauw GJ, Murphy MB *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**: 1623–1630.
38. Shepherd J, Blauw GJ, Murphy MB *et al.* The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am J Cardiol* 1999; **84**: 1192–1197.
39. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; **288**: 2998–3007.
40. National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–3421.
41. Tonelli M, Moye L, Sacks FM *et al.* Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 2003; **138**: 98–104.
42. Kidney Disease Outcomes Quality Initiative. K/DOQI Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease. *Am J Kidney Dis* 2003; **41**: S39–S58.
43. Grundy SM, Cleeman JI, Merz CN *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227–239.
44. Colhoun HM, Thomason MJ, Mackness MI *et al.* Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med* 2002; **19**: 201–211.
45. Mason NA, Bailie GR, Satayathum S *et al.* HMG-coenzyme a reductase inhibitor use is associated with mortality reduction in hemodialysis patients. *Am J Kidney Dis* 2005; **45**: 119–126.
46. Waters DD, Guyton JR, Herrington DM *et al.* Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004; **93**: 154–158.
47. Hemmelgarn BR, McAlister FA, Grover S *et al.* The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension: Part I–Blood pressure measurement, diagnosis and assessment of risk. *Can J Cardiol* 2006; **22**: 573–581.
48. McPherson R, Frohlich J, Fodor G *et al.* Canadian Cardiovascular Society position statement—recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006; **22**: 913–927.
49. Buse JB, Ginsberg HN, Bakris GL *et al.* Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007; **30**: 162–172.